UNITED STATES PATENT APPLICATION

FOR

ACYLATED 1,2,3,4-TETRAHYDRONAPHTHYL AMINES AND THEIR USE AS PHARMACEUTICAL AGENTS

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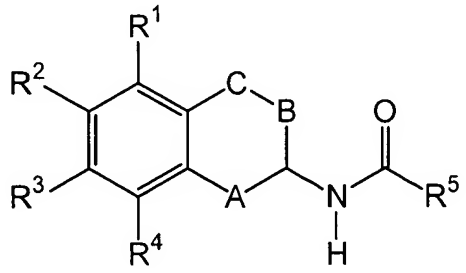
[01] The present invention relates to acylated 1,2,3,4-tetrahydronaphthyl amines of the general formula (I), with the definitions of R^1 to R^5 and A, B and C given below in the text, in any of their stereoisomeric forms or mixtures thereof in any ratio or the pharmaceutically acceptable salts thereof and their use as pharmaceutical agents.

[02]



(I)

[03] Endothelial NO synthase (eNOS, NOS-III) belongs to a group of three isoenzymes which produce nitric oxide (NO) by oxidation of arginine. Endothelially released NO is of central importance in a number of key cardiovascular mechanisms. It has a vasodilating effect and inhibits the aggregation of platelets, the adhesion of leukocytes to the endothelium and the proliferation of intimal smooth muscle cells.

[04] Endothelial NO synthase is subject to physiological and pathophysiological regulation both at the transcriptional and at the post-transcriptional level. Enzyme already present in the endothelium may undergo calcium-dependent and calcium-independent activation through phosphorylation of specific amino acids, but also by direct interactions with specific proteins. Stimulators of this, usually transient, NO release are, extracellular arginine, 17β-estrogen and the mechanical stimulus exerted on the luminal surface of the

endothelium by the blood flow (shear stress). The latter additionally leads to regulation of eNOS at the transcriptional level. Thus, for example, Sessa et al. (Circ. Research 74 (1994) 349-353) were able by means of exercise training and the increase in shear stress associated therewith to obtain a marked increase in ecNOS.

[05] Whether regulation at the post-transcriptional level is relevant in vivo, is not unambiguously proved. Thus, for example, administration of a high arginine dose is followed by only a transient improvement in the endothelium-dependent vasorelaxation in patients with coronary heart disease.

[06] On the other hand, the significance of the upregulation of the eNOS protein is scientifically accepted. Thus, there are findings which show that the protective properties of the HMG-CoA reductase inhibitor simvastatin can be attributed, besides the lipid lowering, also in part to an increase in eNOS expression in vivo (Endres et al., Proc. Natl. Acad. Sci. USA 95 (1998) 8880-8885). It is additionally known that single point mutations in the 5'-flanking region of the eNOS gene ("eNOS promoter"), and the reduction in the rate of eNOS gene transcription associated therewith, in the Japanese population is associated with an increase in the risk of coronary spasms (Nakayama et al., Circulation 99 (1999) 2864-2870).

[07] The current assumption therefore is that the transcriptional and post-transcriptional mechanisms of eNOS regulation are seriously disturbed in a large number of disorders, especially in cardiovascular disorders. Even in very early stages of a wide variety of cardiovascular disorders it is possible for a dysfunction of this type in the endothelium lining the blood vessels to lead to a deficiency of bioactive NO, which is manifested as the disorder progresses in the form of measurable pathophysiological and morphological

disorder progresses in the form of measurable pathophysiological and morphological changes. Thus, critical steps in early atherogenesis are speeded up by a decrease in endothelial NO release, such as, for example, the oxidation of low density lipoproteins, the recruitment and deposition of monocytes in the intima of vessels, and the proliferation of intimal cells. A consequence of atherogenesis is the formation of plaques on the inside of the blood vessels, which may in turn lead, through a diminution in the shear stress, to a further decrease in endothelial NO release and a further deterioration in the pathology. Since endothelial NO is also a vasodilator, a decrease thereof frequently also leads to hypertension, which may, as an independent risk factor, cause further organ damage.

[08] The aim of a therapeutic approach to the treatment of these disorders must accordingly be to interrupt this chain of events by increasing the endothelial NO expression. Gene transfer experiments which lead in vitro to overexpression of NO synthase in previously damaged vessels are in fact able to counteract the described processes and are thus evidence of the correctness of this approach (Varenne et al., Hum. Gene Ther. 11 (2000) 1329).

[09] Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. The statins which have already been mentioned are, however, the only substances for which it has been possible to date to show such an increase in eNOS in vivo as a side effect. In view of the known range of side effects of this class of substances, however, it is unclear how far this effect is present in a toxicologically unproblematic dose.

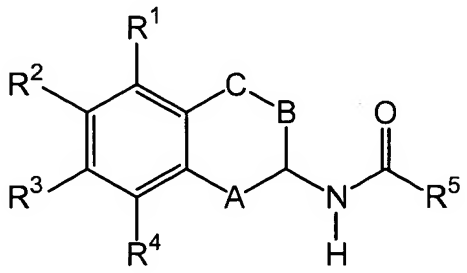
[010] Liao et al. claim in WO 99/47153 and WO 00/03746 the use of rhoGTPase inhibitors and agents which influence the organization of the actin cytoskeleton for increasing eNOS

in endothelial cells and for the therapy of various disorders such as, for example, strokes or pulmonary hypertension, without, however, indicating a specific way of achieving this.

[011] Thus, there exists a strong need for compounds which upregulate eNOS-expression in endothelial cells. The object of the present invention is to provide compounds showing this ability.

[012] This object is attained by acylated 1,2,3,4-tetrahydronaphthyl amines according to the general formula (I) in any of their stereoisomeric forms or mixtures thereof in any ratio or the pharmaceutically acceptable salts thereof.

[013]



(I)

[014] In the above formula (I),

[015] R^1 and R^4 are independently of each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_8-alkoxy, (C_1-C_8-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl,

C_1-C_3- alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogens; pseudohalogens; $NR^{13}R^{14}$; OR^{15} ; $S(O)_mR^{16}$; $SO^2NR^{17}R^{18}$; and NO_2;

[016] R^2 and R^3 are independently from each other selected from the group consisting of: H; halogens; pseudohalogens; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_{10}-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O--, unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents, of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogens and methoxy;

[017] A is selected from the group consisting of CH_2, CHOH and CH-(C_1-C_3-alkyl);

[018] B is selected from the group consisting of CH_2 and CH-(C_1-C_3-alkyl);

[019] C independently has the same meaning as B;

[020] R^5 is a group Hetar which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogens; pseudohalogens; NH_2; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)amino, di(C_1-C_{10}-alkyl)amino, the substituents of which are selected from the group consisting of F, OH, C_1-C_8-alkoxy, aryloxy, (C_1-C_8-alkyl)mercapto, NH_2, (C_1-C_8-alkyl)amino, and di(C_1-C_8-alkyl)amino; C_3-C_5-alkandiyl; phenyl; heteroaryl; aryl- or heteroaryl-substituted C_1-C_4-alkyl; CF_3; NO_2; OH; phenoxy; benzyloxy; (C_1-C_{10}-alkyl)COO;

$S(O)_mR^{20}$; SH; phenylamino; benzylamino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_4-alkyl)-; phenyl-CONH-; phenyl-CON(C_1-C_4-alkyl)-; heteroaryl-CONH-; heteroaryl-CON(C_1-C_4-alkyl)-; (C_1-C_{10}-alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; $COOR^{21}$; $CONR^{22}R^{23}$; $CNH(NH_2)$; $SO_2NR^{24}R^{25}$; R^{26} SO_2NH-; $R^{27}SO_2N$(C_1-C_6-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O and S, which heterocycles can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said heterocycles can optionally be condensed to the said group Hetar; wherein all aryl, heteroaryl, phenyl, aryl-containing, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[021] R^6 is selected from the group consisting of:

H; C_1-C_{10}-alkyl, which can be substituted by one or more substituents selected from the group consisting of F, C_1-C_8-alkoxy, and di(C_1-C_8-alkyl)amino; aryl-(C_1-C_4-alkyl) and heteroaryl-(C_1-C_4-alkyl), which can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_4-alkoxy, and di(C_1-C_6-alkyl)amino;

[022] R^7 is selected from the group consisting of:

H; C_1-C_{10}-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C_1-C_8-alkoxy, di(C_1-C_8-alkyl)amino and phenyl; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted

or carry one or more substituents from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

[023] R^8 is H or C_1-C_{10}-alkyl;

[024] R^9 is selected from the group consisting of: C_1-C_{10}-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F, (C_1-C_4)-alkoxy, di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogens, pseudohalogens, and CF_3;

[025] R^{10} independently has the same meaning as R^7;

[026] R^{11} independently has the same meaning as R^8 ;

[027] R^{12} independently has the same meaning as R^6;

[028] R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; unsubstituted and substituted phenyl, benzyl, heteroaryl, (C_1-C_6-alkyl)-CO, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[029] R^{14} independently has the same meaning as R^{13};

[030] R^{15} is selected from the group consisting of: H; C_1-C_{10}-alkyl; (C_1-C_3-alkoxy)-C_1-C_3-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[031] R^{16} is selected from the group consisting of: C_1-C_{10}-alkyl which can be substituted by one or more substituents selected from the group consisting of F, OH, C_1-C_8-alkoxy, aryloxy, (C_1-C_8-alkyl)mercapto, (C_1-C_8-alkyl)amino and di(C_1-C_8-alkyl)amino; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, and wherein one or more of these substitutents can be present;

[032] R^{17} independently has the same meaning as R^7;

[033] R^{18} independently has the same meaning as R^8;

[034] R^{19} independently has the same meaning as R^{16};

[035] R^{20} independently has the same meaning as R^{16};

[036] R^{21} independently has the same meaning as R^6;

[037] R^{22} independently has the same meaning as R^7;

[038] R^{23} independently has the same meaning as R^8;

[039] R^{24} independently has the same meaning as R^7;

[040] R^{25} independently has the same meaning as R^8;

[041] R^{26} independently has the same meaning as R^{16};

[042] R^{27} independently has the same meaning as R^{16};

[043] heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

[044] the group Hetar is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

[045] aryl is phenyl, naphth-1-yl or naphth-2-yl; and

[046] m is 0, 1 or 2;

[047] with the proviso that, in case R^1, R^2, R^3 and R^4 are hydrogen or one of the substituents, R^1, R^2, R^3 or R^4 is C_1-C_6-alkoxy, R^5 is not unsubstituted pyridyl or unsubstituted or substituted 4-oxoquinolinyl.

[048] If, in the compounds of formula (I), groups or substituents such as, for example, aryl, heteroaryl, alkyl etc., can be present several times, they all independently from each other have the meanings indicated and can hence, in each individual case, be identical with or different from each other. One example is the di(C_1-C_{10}-alkyl)amino group in which the alkyl substitutents can be identical or different.

[049] Alkyl, alkenyl and alkynyl residues can be linear or branched, acyclic or cyclic. This also applies when they are part of other groups, for example in alkoxy groups, alkoxycarbonyl groups or amino groups, or when they are substituted.

[050] Examples for alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here also expressly includes cycloalkyl residues and cycloalkyl-alkyl -residues (alkyl substituted by cycloalkyl) containing at least three carbon atoms. Examples for such cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooetyl. All cycloalkyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl. Examples for substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example, aryl groups. In substituted alkyl residues, for example arylalkyl, hydroxyalkyl such as

-(C_1-C_3)-alkyl-OH or alkoxyalkyl such as -(C_1C_3)-alkyl-O-(C_1-C_4)-alkyl, the substituents can be present in any desired position.

[051] Examples for alkenyl and alkynyl groups are the vinyl residue, the 1-propenyl residue, the 2-propenyl residue (allyl residue), the 2-butenyl residue, the 2-methyl-2-propenyl residue, the 3-methyl-2-butenyl residue, the ethynyl residue, the 2-propynyl residue (propargyl residue), the 2-butynyl residue or the 3-butynyl residue. The term alkenyl here also expressly includes cycloalkenyl residues and cycloalkenyl-alkyl-residues (alkyl substituted by cycloalkenyl) containing at least three carbon atoms. Examples for cycloalkenyl residues are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. All cycloalkenyl groups can be substituted by one or more identical or different (C_1-C_4)-alkyl residues, in particular by methyl. Furthermore, unless stated otherwise, the term alkenyl and alkynyl here also includes unsubstituted alkenyl and alkynyl residues as well as alkenyl and alkynyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkenyl and alkynyl residues, for example, arylalkenyl, hydroxyalkenyl such as -(C_2-C_3)alkenyl-OH or alkoxyalkenyl such as (C_1-C_3-alkyl)-O-(C_2-C_4-alkenyl)-, the substituents can be present in any desired position.

[052] Examples for C_3-C_5-alkandiyl are $-CH_2CH_2CH_2-$, $-CH_2-CH(CH_3)$, $-CH_2CH_2CH_2CH_2-$ and $-CH_2CH_2CH_2CH_2CH_2-$ groups.

[053] If not stated otherwise, the above-mentioned phenyl residues, naphthyl and indanyl residues and heterocyclic residues (including heteroaryl residues) can be unsubstituted or can carry one or more, for example one, two, three or four, of the substituents indicated in the above definition which can be in any desired position. If in compounds of the formula

(I) nitro groups are present as substituents, in total only up to two nitro groups are preferably present in the molecule. In monosubstituted phenyl residues the substituent can be in the 2-position, the 3-position or the 4-position, in disubstituted phenyl residues the substituents can be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. In fourfold substituted phenyl residues, the substituents can be in the 2,3,4,5 -position, the 2,3,4,6-position, or the 2, 3,5,6-position. Tolyl (= methylphenyl) can be 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position; in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions. Indanyl residues include indan-1-yl residues and indan-2-yl residues which can be unsubstituted or carry one or more of the substituents indicated. In case the indanyl residues are substituted, the substituent or substituents can be in any of the positions possible.

[054] The above definitions as well as the following definitions relating to monovalent residues equally apply to the divalent residues phenylene, naphthylene and heteroarylene. Those divalent residues can be attached to the adjacent groups by any ring carbon atom. In the case of a phenylene residue, these can be in 1,2-position (ortho-phenylene), 1,3-position (meta-phenylene) or 1,4-position (para-phenylene). In the case of a

naphthylene residue the free bonds can be in 1,2-position (= 1,2-naphthylene or 1,2-naphthalinediyl) or in 1,3position, 1,4-position, 1,5-position, 1,6-position, 1,7-position, 1,8-position, 2,3-position, 2,6-position or 2,7-position. In the case of 5-membered ring aromatics containing one heteroatom such as, for example, thiophene or furan, the two free bonds can be in 2,3 position, 2,4-position, 2,5-position or 3,4-position. A divalent residue derived from pyridine can be a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-pyridinediyl residue. In the case of unsymmetrical divalent residues, the present invention includes all positional isomers, i. e., in the case of a 2,3-pyridinediyl residue, for example, it includes the compound in which the one adjacent group is present in the 2-position and the other adjacent group is present in the 3-position as well as the compound in which the one adjacent group is present in the 3-position and the other adjacent group is present in the 2-position.

[055] Unless stated otherwise, heteroaryl residues, heteroarylene residues, heterocyclyl residues and rings which are formed by two groups bonded to a nitrogen are preferably derived from heterocycles which contain one, two, three or four heteroatoms which can be identical or different; more preferably they are derived from heterocycles which contain one, two, or three, in particular one or two, heteroatoms which can be identical or different. Unless stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic. The rings preferably are 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which residues occurring in the compounds of the formula (I) can be derived, are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole (= oxazole), 1,2-oxazole (=

isoxazole), 1,3-thiazole (= thiazole), 1,2-thiazole (= isothiazole), tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, benzodioxol, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridin, or phenothiazine, each of them in saturated form (perhydro form) or in partially unsaturated form (for example in the dihydro form or the tetrahydro form) or in maximally unsaturated form, in case the respective forms are known and stable. The term "aryl" and the term "heteroaryl" as used herein comprise bicyclic residues in which both cycles are aromatic as well as bicyclic residues in which only one cycle is aromatic. Independently, the same applies to the term "group Ar" or the term "group Hetar", respectively. Suitable heterocycles include, for example, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in their individual definitions. Unsaturated heterocycles can contain, for example, one, two or three double bonds within the ring system. 5-membered rings and 6-membered rings can in particular also be aromatic.

[056] Substituents which may be derived from these heterocycles can be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles can carry a hydrogen atom or a substituent on a ring nitrogen atom, and examples include pyrrole, imidazole, pyrrolidine, morpholine, piperazine residues, etc. Those nitrogen heterocyclic residues can also be attached via a ring nitrogen atom, in particular if the respective heterocyclic residue

is bonded to a carbon atom. For example, a thienyl residue can be present as 2-thienyl residue or 3-thienyl residue, a furyl residue as 2-furyl residue or 3-furyl residue, a pyridyl residue as 2-pyridyl residue, 3-pyridyl residue or 4-pyridyl residue, a piperidinyl residue as 1-piperidinyl residue (= piperidino residue), 2-piperidinyl residue, 3-piperidinyl residue or 4-piperidinyl residue, a (thio)morpholinyl residue as 2-(thio)morpholinyl residue, 3-(thio)morpholinyl residue or 4-(thio)morpholinyl residue (= thiomorpholino residue). A residue derived from 1,3-thiazole or imidazole which is attached via a carbon atom can be attached via the 2-position, the 4-position or the 5-position.

[057] In case a heterocyclic group is substituted, it can carry one or more, for example one, two, three or four, identical or different substituents. Substituents in heterocycles can be present in any desired positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. Suitable nitrogen heterocycles can also be present as N-oxides or as quarternary salts containing a counterion which is derived from a pharmaceutically acceptable acid. Pyridyl residues, for example, can be present as pyridine-N-oxides.

[058] Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine.

[059] Examples for pseudohalogens are CN and N_3, a preferred pseudohalogen is CN.

[060] The present invention includes all stereoisomeric forms of the compounds of the formula (I). Centers of asymmetry that are present in the compounds of formula (I) all independently of one another have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the present invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. All these forms are an object of the present invention. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochernically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula (I) or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

[061] In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts,

alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids [062] . Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art.

[063] If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art as, for example, by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts.

[064] The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

[065] The present invention furthermore includes all solvates of compounds of the formula (I), for example hydrates or adducts with alcohols, active metabolites of the compounds of the formula (II), and also derivatives and prodrugs of the compounds of the formula (I) which contain physiologically tolerable and cleavable groups, for example esters, amides and compounds in which the N-H group depicted in formula (I) is replaced with an N-alkyl group, such as N-methyl, or with an N-acyl group, such as N-acetyl or N-argininyl, including pharmaceutically acceptable salts formed on functional groups present in the Nacyl group.

[066] Preferred compounds of the formula (I) are those compounds in which one or more, including all, of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

[067] In preferred embodiments of the present invention, the substituents R^1 to R^5 , A, B and C and the groups aryl and heteroaryl of the formula (I) independently of each other have the following meanings. Hence, one or more of the substituents R^1 to R^5 and A, B and C can have the preferred meanings, the more preferred meanings, the even more preferred meanings, the most preferred meanings, or the particularly preferred meanings given below.

[068] R^1 is preferably selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogens; pseudohalogens; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where

heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S; R^1 is more preferably H, halogen or C_1-C_4-alkyl.

[069] R^2 is preferably selected from the group consisting of: H; halogens; pseudohalogens; and C_1-C_3 -alkyl; R^2 is more preferably H.

[070] R^3 is preferably selected from the group consisting of: H; halogens; pseudohalogens; and C_1-C_3-alkyl; R^3 is more preferably H.

[071] R^4 is preferably selected from the group consisting of: -H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogens; pseudohalogens; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S; R^4 is more preferably H, halogen or C_1 -C_4-alkyl; R^4 is most preferably H.

[072] R^1 to R^4 are in particular each H.

[073] A is preferably selected from the group consisting of CH_2 and CHOH; A is in particular CH_2.

[074] B and C are preferably independently of each other selected from the group consisting of CH_2 and CH-CH_3; more preferably B is a CH_2 unit while C is CH_2 or CH-CH_3; Most preferably B and C are CH_2.

[075] R^5 is preferably a group Hetar which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogens; CN; NH_2; unsubstituted and at least monosubstituted C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, (C_1-C_8-

alkyl)amino, di(C_1-C_8-alkyl)amino, the substituents of which are selected from the group consisting of F, C_1-C_6-alkoxy, phenoxy, (C_1-C_6-alkyl)mercapto, NH_2, (C_1-C_6-alkyl)amino, and di(C_1-C_6-alkyl)amino; C_3-C_5-alkandiyl; phenyl; heteroaryl; phenyl- or heteroaryl-substituted C_1-C_2-alkyl; CF_3; OH; phenoxy; benzyloxy; (C_1-C_6-alkyl)COO; $S(O)_m$(C_1-C_6)-alkyl; $S(O)_m$-phenyl; $S(O)_m$-heteroaryl; SH; phenylamino; benzylamino; (C_1-C_6-alkyl)-CONH-; (C_1-C_6-alkyl)-CON(C_1-C_4-alkyl)-; phenyl-CONH-; phenyl-CON(C_1-C_4-alkyl)--, heteroaryl-CONH-; heteroaryl-CON(C_1-C_4-alkyl)-; (C_1-C_6-alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; COO(C_1-C_6alkyl); -$CONH_2$; -CONH(C_1-C_6-alkyl); -CON(di(C_1-C_6-alkyl)); CNH(NH_2); -SO_2NH_2; -SO_2NH(C_1-C_6-alkyl); -SO_2NH(phenyl); -SO_2N(di(C_1-C_6-alkyl)); (C_1-C_6-alkyl)SO_2NH-; (C_1-C_6-alkyl)SO_2N(C_1-C_6-alkyl)-; phenyl-SO_2NH-; phenyl-SO_2N(C_1-C_6-alkyl)-; heteroaryl-SO_2NH-; heteroaryl-SO_2N(C_1-C_6-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, which heterocycles can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said heterocycles can optionally be condensed to the said group Ar or the said group Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[076] R^5 is more preferably a group Hetar which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogens; CN; NH_2; unsubstituted

and at least monosubstituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_3-alkoxy, (C_1-C_4alkyl)amino, di(C_1-C_4-alkyl)amino, the substituents of which are selected from the group consisting of F, C_1-C_3-alkoxy, (C_1-C_3-alkyl)mercapto, and NH_2; C_3-C_5-alkandiyl; phenyl; heteroaryl; phenyl- or heteroaryl- substituted C_1-C_2-alkyl; CF_3; OH; (C_1-C_4-alkyl)COO; $S(O)_m$(C_1-C_4)-alkyl; (C_1-C_4-alkyl)-CONH-; (C_1-C_4-alkyl)-CON(C_1-C_4-alkyl)-; (C_1-C_4alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; COO(C_1-C_6-alkyl); -$CONH_2$; -CONH(C_1-C_4-alkyl); -CON(di(C_1-C_4-alkyl)); CNH(NH_2); -SO_2NH_2; -SO_2NH(C_1-C_4-alkyl); -SO_2NH(phenyl); -SO_2N(di(C_1-C_4-alkyl)); (C_1-C_4-alkyl)SO_2NH-; (C_1-C_4-alkyl)SO_2N(C_1-C_4-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, which heterocycles can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said heterocycles can optionally be condensed to the said phenyl or the said group Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[077] R^5 is even more preferably a group Hetar which can be unsubstituted or carry one or more substituents selected from the group consisting of. F; Cl; Br; C_1-C_3-alkyl; C_1-C_3-alkoxymethyl; 2-amino-3,3,3-trifluoro-propyl-; CF_3; C_3-C_5-alkandiyl; phenyl; heteroaryl; benzyl; heteroaryl-methyl; OH; C_1-C_3-alkoxy; phenoxy; trifluoromethoxy; 2,2,2-

trifluoroethoxy; (C_1-C_4-alkyl)COO; (C_1-C_3-alkyl)mercapto; phenylmercapto; (C_1-C_3-alkyl)sulfonyl; phenylsulfonyl; NH_2; (C_1-C_4-alkyl)amino; di(C_1-C_4-alkyl)amino; (C_1-C_3-alkyl)-CONH-; (C_1-C_3-alkyl)-SO_2NH-; (C_1-C_3-alkyl)-CO; phenyl-CO; -OCH_2O-; -OCF_2O; -CH_2CH_2O-; COO(C_1-C_4-alkyl); -$CONH_2$; -CONH(C_1-C_4-alkyl); -CON(di(C_1-C_4-alkyl)); CN; -SO_2NH_2; -SO_2NH(C_1-C_4-alkyl); -SO_2N(di(C_1-C_4-alkyl)); pyrrolidinyl; piperidinyl; morpholinyl; and thiomorpholinyl; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[078] R^5 is most preferably selected from the group consisting of. benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzofuran-5-yl, 1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-yl, 1-(4-fluoro-phenyl)-3,5-dimethyl-1H-pyrazole-4-yl, 1H-benzotriazole-5-yl, 1H-indole-4-yl, 1H-indole-6-yl, 1-isopropyl-2-trifluoromethyl-1H-benzoimidazole-5-yl, 1-methyl-3-oxo-1.2,3,4-tetrahydro-quinoxaline-6-yl, 1-phenyl-5-trifluoromethyl-1H-pyrazole-4-yl, 2-(2-hydroxy-pyridin-4-yl)-1H-benzoimidazole-5-yl, 2-(4-cyano-phenyl)-1H-benzoimidazole-5-yl, 2,4-dimethyl-oxazole-5-yl, 2,4-dimethyl-pyrimidine-5-yl, 2,4-dimethyl-thiazole-5-yl, 2,5-dimethyl-1H-pyrrole-3-yl, 2,5-dimethyl-1-phenyl-1H-pyrrole-3-yl, 2,5-dimethyl-1-pyridin-4-ylmethyl-1H-pyrrolyl, 2,5-dimethyl-2H-pyrazole-3-yl, 2,6-dichloro-pyrid-3-yl, 2,6-dimethoxy-pyrid-3-yl, 2,6-dimethyl-pyrid-3-yl,2-amino-4,6-dimethyl-pyrid-3-yl, 2-amino-6-chloro-pyrid-3-yl, 2-amino-pyrid-3-yl, 2-chloro-6-methyl-pyrid-3-yl, 2-chloro-pyrid-4-yl, 2-cyclopropyl-4-methyl-thiazole-5-yl, 2-dimethylamino-4-methyl-thiazole-5-yl, 2-dimethylamino-pyrid-4-yl, 2-ethyl-5-methyl-2H-

pyrazole-3-yl, 2-hydroxy-6-methyl-pyrid-3-yl, 2-methyl-1H-benzoimidazole-5-yl, 2-methyl-3H-benzoimidazole-5-yl, 2-methyl-pyrid-3-yl, 2-methyl-6-trifluoromethyl-pyrid-3-yl, 2-methyl-thiazole-5-yl, 2-morpholin-4-yl-pyridin-4-yl, 2-morpholin-4-yl-pyrimidine-5yl, 2-pyrrolidin-1-yl-pyridin-4-yl, 3,5-dimethyl-1H-pyrazole-4-yl, 3-amino-5,6-dimethyl-pyrazine-2-yl, 3-amino-5-methyl-pyrazine-2-yl, 3-amino-pyrazine-2-yl, 3H-benzoimidazole-5-yl, 1H-benzoimidazole-5-yl, 3-methyl-isoxazole-4-yl, 4,6-dimethylpyrid-3-yl, 4-amino-2-ethylsulfanyl-pyrimidine-5-yl, 4-amino-2-methyl-pyrimidine-5-yl, 4-methyl-thiazole-5-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, 5-thiophen-2-yl-pyrid3-yl, 2-methyl-4-trifluoromethyl-thiazol-5-yl, 5,6,7,8-tetrahydro-quinoline-3-yl, 5-amino1-phenyl-1H-pyrazole-4-yl, 5-methyl-1-phenyl-1H-pyrazole-4-yl, 5-methyl-isoxazole-3-yl, 5-methyl-pyrid-3-yl, 5-methyl-pyrazine-2-yl, 6-chloro-pyrid-3-yl, 6-cyano-pyrid-3-yl, 6-dimethylamino-pyrid-3-yl, 6-ethynyl-pyrid-3-yl, 6-methoxymethyl-pyrid-3-yl, 6-methoxypyrid-3-yl, 6-methyl-2-methylamino-pyrid-3-yl, 6-methylamino-pyrazine-2-yl, 6-methylpyrid-3 -yl, 6-morpholin-4-yl-pyrid-3-yl, 6-pyrrolidin-1 -yl -pyrid-3 -yl, imidazo[1,2a]lpyridine-2-yl, 6-trifluoromethyl-pyrid-3-yl, and pyrimidine-4-yl.

[079] Heteroaryl is preferably a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one, two or three heteroatoms selected from the group consisting of N, O, and S; heteroaryl is most preferably selected from the group consisting of: furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzoimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofuranyl, benzothiophenyl, and indazolyl.

[080] The group Hetar is preferably a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one, two or three heteroatoms selected from the group consisting of

N, O, and S; the group Hetar is most preferably selected from the group consisting of: furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzoimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofaranyl, benzothiophenyl, and indazolyl.

[081] Aryl is preferably phenyl.

[082] m is preferably 0 or 2.

[083] Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred meanings, the more preferred meanings, the even more preferred meanings, the most preferred meanings, or the particularly preferred meanings defined above are also an object of the present invention.

[084] In another embodiment of the present invention, the substituents R^1 to R^5 , A, B and C and the groups aryl and heteroaryl according to the formula (I) have the following meanings.

[085] R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10},R^{11}$, $COOR^{12}$; CF_3; halogens; pseudohalogens; $NR^{13}R^{14}$; OR^{15} ; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

[086] R^2 and R^3 are independently of each other selected from the group consisting of: H; halogens; pseudohalogens; unsubstituted and at least monosubstituted C_1-C_6-alkyl, the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-,. unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogens and methoxy;

[087] A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

[088] B is CH_2 or CH-(C_1 -C_3-alkyl);

[089] C independently has the same meaning as B;

[090] R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of. halogens; pseudohalogens; C_1-C_{10}alkyl; C_3-C_5-alkandiyl; phenyl; phenyl substituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_m$ R^{20}; (C_1-C_{10}-alkyl)amino; di(C_1C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}alkyl)-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH2O-; -CH_2CH2O-; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5-to-7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O, and S which can be substituted by one or more substituents from the group consisting of halogens,

C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3; where with respect to the group R^5 which can be an aryl or a heteroaryl group, a heteroaryl group is generally preferred over an aryl group, and said heteroaryl group can be unsubstituted or substituted and carry at least one of the substituents mentioned above in the definition relating to R^5;

[091] R^6 is H, C_1 -C_6-alkyl or benzyl;

[092] R^7 is selected from the group consisting of:

H; C_1-C_6-alkyl which can be phenyl -substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

[093] R^8 is H or C_1-C_6-alkyl;

[094] R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogens, pseudohalogens, and CF_3;

[095] R^{10} independently has the same meaning as R^7;

[096] R^{11} independently has the same meaning as R^8;

[097] R^{12} independently has the same meaning as R^6;

[098] R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of

which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[099] R^{14} is H or C_1-C_6-alkyl;

[0100] R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[0101] R^{16} is selected from the group consisting of: -C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

[0102] R^{17} independently has the same meaning as R^7;

[0103] R^{18} independently has the same meaning as R^8;

[0104] R^{19} independently has the same meaning as R^{16};

[0105] R^{20} independently has the same meaning as R^{16};

[0106] R^{21} independently has the same meaning as R^6;

[0107] R^{22} independently has the same meaning as R^7;

[0108] R^{23} independently has the same meaning as R^8;

[0109] R^{24} independently has the same meaning as R^7;

[0110] R^{25} independently has the same meaning as R^8;

[0111] heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O, and S;

[0112] aryl is phenyl, naphth-1-yl or naphth-2-yl;

[0113] m is 0, 1 or 2,

[0114] with the proviso that, in case R^1, R^2, R^3 and R^4 are hydrogen, R^5 is not phenyl, 5-chloro-2-ethoxyphenyl, 5-chloro-2-methoxyphenyl, 5-bromo-2-methoxyphenyl, 5-fluoro-2-methoxyphenyl, 2-methoxy-5-methylphenyl, 3-alkylcarbonylamino-2-hydroxyphenyl or unsubstituted or substituted 4-oxoquinolinyl; and that, in case R^5 is phenyl, A is not CHOH; and that, in case R^5 is phenyl, R^1 is not hydroxy or methoxy; and that, in case R^5 is phenyl, R^2 is not Br, hydroxy or methoxy; and that, in case R^5 is 3-pyridyl, R^2 is not hydroxy.

[0115] The compounds according to general formula (I) and their precursors can be prepared according to methods published in the literature or, respectively, analogous methods. Appropriate methods have been published in, for example, Windaus; Chem.Ber. 57 (1924) 1735, Cannon, J.G. et al, J.Med.Chem. 17 (1974) 565, Itoh, K. et al., Chem.Pharm. Bull. 25 (1977) 2917, Hillver et al, J.Med.Chem. 33 (1990) 1541, Copinga et al., J.Med.Chem. 36 (1993) 2891 and Trillat et al., Eur.J.Med.Chem.Chim.Ther. 33 (1998) 437. 1,2,3,4-Tetrahydronaphthyl amines prepared according to the disclosed methods can be dissolved in a solvent such as, for example, dichloromethane, THF, toluene or dioxane and reacted in the presence of base such as, for example, triethylamine, with an appropriate carboxylic acid derivative, for example, a carboxylic acid chloride. This reaction is preferably carried out at room temperature.

[0116] Alternatively, the compounds according to the general formula (I) are obtained by a coupling reaction of the respective 1,2,3,4-tetrahydronaphthyl amines with an acid, which 1,2,3,4-tetrahydronaphthyl amines and/or acid may be substituted and/or functionalized, in the presence of a base like, for example, diisopropylethylamine, and the use of an appropriate coupling reagent like, for example, carbodiimides, HATU or TOTU. The thus

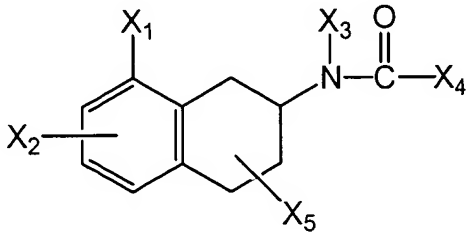
obtained acyl 1,2,3,4-tetrahydronaphthyl amines can then be functionalized, in order to obtain further desired compounds according to the general formula (I). The reaction leading to the above-mentioned acyl 1,2,3,4-tetrahydronaphthyl amines and the reactions used in the functionalization are known to the person skilled in the art.

[0117] All reactions for the synthesis of the compounds of the formula (I) are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of the formula (I), it can be necessary or advantageous to temporarily block functional groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later reaction step are converted into the desired functional groups. Such synthesis strategies and protective groups and precursor groups which are suitable in an individual case are known to the skilled person. If desired, the compounds of the formula (I) can be purified by customary purification procedures, for example by recrystallization or chromatography. The starting compounds for the preparation of the compounds of the formula (I) are commercially available or can be prepared according to or analogously to literature procedures. The compounds obtained with the above-mentioned synthesis methods are a further object of the present invention.

[0118] Some of the compounds falling under formula (I) and their use as pharmaceutical agents are disclosed in the literature.

[0119] EP-A 0 253 257 discloses various acylated 1,2,3,4-tetrahydronaphthyl amines falling under the general formula I and their use as precursors for the synthesis of pharmacologically active compounds.

[0120] EP-A 0 420 064 discloses the use of various compounds according to the general formula I for therapeutic and diagnostic purposes like insomnia and psychic diseases. The treatment of cardiovascular diseases is not disclosed. Compounds disclosed by EP-A 0 420 064 include 2-amidotetralin derivatives of the general formula (II).



(II)

In the above formula, X_1 - X_5 have the following meaning:

X_1 is hydrogen, halogen, amino, amido, a C_{1-4} alkyl, alkoxyl, or alkoxylaryl;

X_2 is hydrogen, hydroxyl, halogen, amino, amido, aryl, mono- or di- C_{1-4} alkylamino, C_{1-4} alkylaryl, or alkoxylaryl, or C_{1-4} alkyl, alkenyl, alkynl, alkoxyl;

X_3 is hydrogen, aryl,C_{1-4} alkylaryl, or C_{1-4} alkyl, alkenyl, or alkynl;

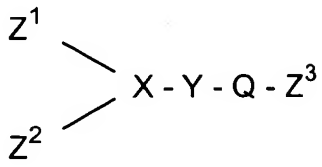
X_4 is aryl, C_{1-4} alkylaryl, or C_{1-4} alkyl, haloalkyl, or cycloalkyl;

X_5 is hydrogen, hydroxyl, halogen, oxo, aryl,C_{1-4} alkylaryl, or C_{1-4} alkyl;

wherein aryl substitutents of X_2, X_3, X_4 and X_5 may optionally be halogen, hydroxyl, amino, mono- or di- C_{1-4} alkylamino, or C_{1-4} alkyl or alkoxyl substituted, provided that when X_1 is methoxy, and X_2, X_3, and X_5 are hydrogen, X_4 is not methyl.

Compounds explicitly disclosed by EP-A 0 420 064 are not an object of the present invention.

[0121] WO 00/51970 discloses compounds according to the general formula (III) and their use for the potentiation of cholinergic activity.



(III)

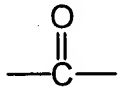
In the above formula:

Z^1 and Z^2 are each aryl or ar(lower)alkyl, or are taken together to form lower alkylene or lower alkenylene, each of which may be substituted with aryl or may be condensed with a cyclic hydrocarbon optionally substituted with lower alkyl, lower alkoxy, aryl, aryloxy or halogen,

Z^3 is lower alkyl, lower alkoxy, aryl, arylamino or aryloxy, each of which may be substituted with lower alkoxy or halogen, pyridyl, or pyridylamino,

X is CH or N,

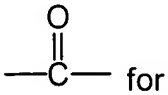
Y is a single bond or -NH-, and

Q is 

[0122] Referring to the definition of Z^1 and Z^2 in formula (III), it is stated that preferred lower alkylenes are tetramethylene or pentamethylene, preferred lower alkenylenes are butenylene, pentenylene or methylpentenylene, a preferred cyclic hydrocarbon is benzene and a preferred aryl is phenyl.

[0123] Furthermore, it is stated that, among other preferred compounds according to the general formula (III) are those having lower alkenylene which may be substituted with aryl

or may be condensed with benzene optionally substituted with lower alkoxy for Z^1 and Z^2 to be taken together to form, aryl or arylamino, each of which may be substituted with halogen, pyridyl, or pyridylamino for Z^3, CH or N for X, a single bond or -NH- for Y, and

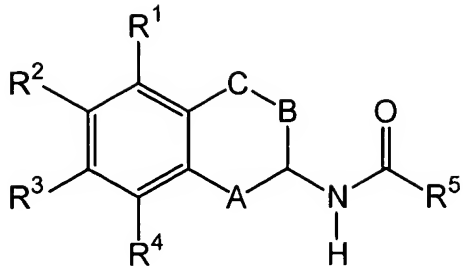
 for Q.

[0124] More preferred compounds according to the general formula (III) are those having Z^1 and Z^2 taken together to form methylpentenylene, butenylene condensed with benzene or pentenylene which may be condensed with benzene optionally substituted with lower alkoxy.

[0125] As examples, there are provided 2-(4-fluorobenzoylamino)-1,2,3,4,-tetrahydronaphthalene, 2-(pyridin-4-ylcarbonylamino)-1,2,3,4-tetrahydronaphthalene, (R)-4-fluoro-N-(1,2,3,4tetrahydronaphthalen-2-yl)-benzamide, (S)-4-fluoro-N-(1,2,3,4-tetrahydronaphthalen-2-yl)-benzamide, 4-fluoro-N-(7-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-benzamide and 4-fluoro-N-(6-methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-benzamide.

[0126] Compounds explicitly disclosed by WO 00/51970 are not an object of the present invention.

[0127] The object of the present invention is furthermore attained by the use of acylated 1,2,3,4-tetrahydronaphthyl amines according to the general formula (I) in any of their stereoisomeric forms or mixtures thereof in any ratio or the pharmaceutically acceptable salts thereof for the manufacture of a medicament for the stimulation of the expression of endothelial NO-synthase.



(I)

[0128] In the above formula,

R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_8-alkoxy, (C_1-C_8-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogens; pseudohalogens; $NR^{13}R^{14}$; OR^{15}; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

[0129] R^2 and R^3 are independently from each other selected from the group consisting of: H; halogens; pseudohalogens; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_{10}-alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3; CN; NO_2; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-;

unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1-C_3-alkyl, halogens and methoxy;

[0130] A is selected from the group consisting of CH_2, CHOH and CH-(C_1-C_3-alkyl);

[0131] B is selected from the group consisting of CH_2 and CH-(C_1-C_3-alkyl);

[0132] C independently has the same meaning as B;

[0133] R^5 is a group Ar or a group Hetar both of which can be unsubstituted or carry one or more substituents selected from the group consisting of. halogens; pseudohalogens; NH_2; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkynyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)amino, di(C_1-C_{10}-alkyl)amino, the substituents of which are selected from the group consisting of F, OH, C_1-C_8-alkoxy, aryloxy, (C_1-C_8-alkyl)mercapto, NH_2, (C_1-C_8-alkyl)amino, and di(C_1-C_8-alkyl)amino; C_3-C_5-alkandiyl; phenyl; heteroaryl; aryl- or heteroaryl-substituted C_1-C_4-alkyl; CF_3; NO_2; OH; phenoxy; benzyloxy; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; SH; phenylamino; benzylamino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_4-alkyl)-; phenyl-CONH-; phenyl-CON(C_1-C_4-alkyl)-; heteroaryl-CONH-; heteroaryl-CON(C_1-C_4-alkyl)-; (C_1-C_{10}-alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; $COOR^{21}$; $CONR^{22}R^{23}$; $CNH(NH_2)$; $SO_2NR^{24}R^{25}$; $R^{26}SO_2NH$-; $R^{27}SO_2N$(C_1-C_6-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O and S, which heterocycles can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said

heterocycles can optionally be condensed to the said group Ar or the said group Hetar; wherein all aryl, heteroaryl, phenyl, aryl-containing, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[0134] R^6 is selected from the group consisting of:

H; C_1-C_{10}-alkyl, which can be substituted by one or more substituents selected from the group consisting of F, C_1-C_8-alkoxy, and di(C_1-C_8-alkyl)amino; aryl-(C_1-C_4-alkyl) and heteroaryl-(C_1-C_4-alkyl), which can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_4-alkoxy, and di(C_1-C_6-alkyl)amino;

[0135] R^7 is selected from the group consisting of:

H; C_1-C_{10}-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C_1-C_8-alkoxy, di(C_1-C_8-alkyl)amino and phenyl; phenyl; indanyl;

[01] and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

[0136] R^8 is H or C_1-C_{10}-alkyl;

[0137] R^9 is selected from the group consisting of: C_1-C_{10}-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F, (C_1-C_4)-alkoxy, di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogens, pseudohalogens, and CF_3;

[0138] R^{10} independently has the same meaning as R^7;

[0139] R^{11} independently has the same meaning as R^8;

[0140] R^{12} independently has the same meaning as R^6;

[0141] R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; unsubstituted and substituted phenyl, benzyl, heteroaryl, (C_1-C_6-alkyl)-CO, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[0142] R^{14} independently has the same meaning as R^{13};

[0143] R^{15} is selected from the group consisting of: H; C_1-C_{10}-alkyl; (C_1-C_3-alkoxy)-C_1-C_3-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[0144] R^{16} is selected from the group consisting of: C_1-C_{10}-alkyl which can be substituted by one or more substituents selected from the group consisting of F, OH, C_1-C_8-alkoxy, aryloxy, (C_1-C_8-alkyl)mercapto, (C_1-C_8-alkyl)amino and di(C_1-C_8-alkyl)amino; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, and wherein one or more of these substitutents can be present;

[0145] R^{17} independently has the same meaning as R^7;

[0146] R^{18} independently has the same meaning as R^8;

[0147] R^{19} independently has the same meaning as R^{16};

[0148] R^{20} independently has the same meaning as R^{16};

[0149] R^{21} independently has the same meaning as R^6;

[0150] R^{22} independently has the same meaning as R^7;

[0151] R^{23} independently has the same meaning as R8;

[0152] R^{24} independently has the same meaning as R^7;

[0153] R^{25} independently has the same meaning as R^8;

[0154] R^{26} independently has the same meaning as R^{16};

[0155] R^{27} independently has the same meaning as R^{16};

[0156] heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O, and S;

[0157] the group Hetar is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O, and S;

[0158] aryl is phenyl, naphth-1-yl or naphth-2-yl;

[0159] the group Ar is pbenyl, naphth-1-yl or naphth-2-yl; and

[0160] m is 0, 1 or 2.

[0161] Furthermore, with respect to the definitions given above in the context of the compounds according to the general formula (I) for use in the manufacture of a medicament, the same explanations as laid out above in the context with the compounds as such apply.

[0162] In preferred embodiments, the object of the present invention is attained by the use of acylated 1,2,3,4-tetrahydronaphthyl amines according to the general formula (I) in any of their stereoisomeric forms or mixtures thereof in any ratio or the pharmaceutically acceptable salts thereof for the manufacture of a medicament for the stimulation of the expression of endothelial NO-synthase, wherein the substituents R^1 to R^5, A, B and C and

the groups aryl and heteroaryl of the formula (I) independently from each other have the following meanings. Hence, one or more of the substituents R^1 to R^5 and A, B and C can have the preferred, the more preferred, the even more preferred, the most preferred or particularly preferred meanings specified below.

[0163] R^1 is preferably selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogens; pseudohalogens; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S; R^1 is more preferably H, halogen or C_1-C_4-alkyl.

[0164] R_2 is preferably selected from the group consisting of: H; halogens; pseudohalogens; and C_1-C_3-alkyl; R^2 is more preferably H.

[0165] R^3 is preferably selected from the group consisting of: H; halogens; pseudohalogens; and C_1-C_3-alkyl; R^3 is more preferably H.

[0166] R^4 is preferably selected from the group consisting of: H; C_1-C_4-alkyl; C_1-C_4-alkoxy; CF_3; halogens; pseudohalogens; (C_1-C_4-alkyl)-$S(O)_m$-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S; R^4 is more preferably H, halogen or C_1-C_4-alkyl; R^4 is most preferably H.

[02] R^1 to R^4 are in particular each H.

[0167] A is preferably selected from the group consisting of CH_2 and CHOH; A is in particular CH_2.

[0168] B and C are preferably independently from each other selected from the group consisting of CH_2 and $CH\text{-}CH_3$; more preferably B is a CH_2 unit while C is CH_2 or $CH\text{-}CH_3$; most preferably B and C are CH_2.

[0169] R^5 is preferably selected from the group consisting of: a group Ar or a group Hetar both of which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogens; CN; NH_2; unsubstituted and at least monosubstituted C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, (C_1-C_8-alkyl)amino, di(C_1-C_8-alkyl)amino, the substituents of which are selected from the group consisting of F, C_1-C_6-alkoxy, phenoxy, (C_1-C_6-alkyl)mercapto, NH_2, (C_1-C_6-alkyl)amino, and di(C_1-C_6-alkyl)amino; C_3-C_5-alkandiyl; phenyl; heteroaryl; phenyl- or heteroaryl-substituted C_1-C_2-alkyl; CF_3; OH; phenoxy; benzyloxy; (C_1-C_6-alkyl)COO; $S(O)_m$(C_1-C_6)-alkyl; $S(O)_m$-phenyl; $S(O)_m$-heteroaryl; SH; phenylamino; benzylamino; (C_1-C_6-alkyl)-CONH-; (C_1-C_6-alkyl)-CON(C_1-C_4-alkyl)-; phenyl-CONH-; phenyl-CON(C_1-C_4-alkyl)-; heteroaryl-CONH-; heteroaryl-CON(C_1-C_4-alkyl)-; (C_1-C_6-alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; $-OCH_2O-$; $-OCF_2O-$; $-OCH_2CH_2O-$; $-CH_2CH_2O-$; COO(C_1-C_6-alkyl); $-CONH_2$; -CONH(C_1-C_6-alkyl); -CON(di(C_1-C_6-alkyl)); CNH(NH_2); $-SO_2NH_2$; $-SO_2NH$(C_1-C_6-alkyl); $-SO_2NH$(phenyl); $-SO_2N$(di(C_1-C_6-alkyl)); (C_1-C_6-alkyl)SO_2NH-; (C_1-C_6-alkyl)SO_2N(C_1-C_6-alkyl)-; phenyl-SO_2NH-; phenyl-SO_2N(C_1-C_6-alkyl)-; heteroaryl-SO_2NH-; heteroaryl-SO_2N(C_1-C_6-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, which heterocycles can be substituted by one or more

substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said heterocycles can optionally be condensed to the said group Ar or the said group Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[0170] R^5 is more preferably selected from the group consisting of: phenyl or a group Hetar both of which can be unsubstituted or carry one or more substituents selected from the group consisting of. halogens; CN; NH_2; unsubstituted and at least monosubstituted C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_3-alkoxy, (C_1-C_4-alkyl)amino, di(C_1-C_4-alkyl)amino, the substituents of which are selected from the group consisting of F, C_1-C_3-alkoxy, (C_1-C_3-alkyl)mercapto, and NH_2; C_3-C_5-alkandiyl; phenyl; heteroaryl; phenyl- or heteroaryl-substituted C_1-C_2-alkyl; CF_3; OH; (C_1-C_4-alkyl)COO; S(O) (C_1-C_4)-alkyl; (C_1-C_4-alkyl)-CONH-; (C_1-C_4-alkyl)-CON(C_1-C_4-alkyl)-; (C_1-C_4-alkyl)-CO; phenyl-CO; heteroaryl-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O0-; -CH_2CH_2O-; COO(C_1-C_6-alkyl); -$CONH_2$; -CONH(C_1-C_4-alkyl); -CON(di(C_1-C_4-alkyl)); CNH(NH_2); -SO_2NH_2; -SO_2NH(C_1-C_4-alkyl); -SO_2NH(phenyl); -SO_2N(di(C_1-C_4-alkyl)); (C_1-C_4-alkyl)SO_2NH-; (C_1-C_4-alkyl)SO_2N(C_1-C_4-alkyl)-; and saturated or at least monounsaturated aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms selected from the group consisting of N, O, and S, which heterocycles can be substituted by one or more substituents selected from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, OH, oxo and CF_3, where said heterocycles can optionally be

condensed to the said phenyl or the said group Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[0171] R^5 is even more preferably selected from the group consisting of: phenyl or a group Hetar both of which can be unsubstituted or carry one or more substituents selected from the group consisting of: F; Cl; Br; C_1-C_3-alkyl; Cl-C_3-alkoxymethyl; 2-amino-3,3,3-trifluoro-propyl; CF_3; C_3-C_5-alkandiyl; phenyl; heteroaryl; benzyl; heteroaryl-methyl; OH; C_1-C_3-alkoxy; phenoxy; trifluoromethoxy; 2,2,2-trifluoroethoxy; (C_1-C_4-alkyl)COO; (C_1-C_3-alkyl)mercapto; phenylmercapto; (C_1-C_3-alkyl)sulfonyl; phenylsulfonyl; NH_2; (C_1-C_4-alkyl)amino; di(C_1-C_4-alkyl)amino; (C_1-C_3-alkyl)-CONH-; (C_1-C_3-alkyl)-SO_2NH-; (C_1-C_3-alkyl)-CO; phenyl-CO; -OCH_2O-; -OCF_2O-; -CH_2CH_2O-; COO(C_1-C_4-alkyl); -$CONH_2$; -CONH(C_1-C_4-alkyl); -CON(di(C_1-C_4-alkyl)); CN; -SO_2NH_2; -SO_2NH(C_1-C_4-alkyl); -SO_2N(di(C_1-C_4-alkyl)); pyrrolidinyl; piperidinyl; morpholinyl; and thiomorpholinyl; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, OH, C_1-C_3-alkoxy, and CF_3;

[0172] R^5 is most preferably selected from the group consisting of: 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-(C_1-C_3-alkoxy)-phenyl, 4-trifluoromethoxyphenyl, 2-bromo-4-fluorophenyl, 2-chloro-4-fluorophenyl, 3,4-dimethylphenyl, 2,4-dimethylphenyl, 4-chloro-2-methylphenyl, 2-hydroxy-4-methylphenyl, 2-hydroxy-4-ethoxyphenyl, 2-

methoxy-4-methylphenyl, 4-phenoxyphenyl, 3-fluoro-4-methylphenyl, benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzofuran-5-yl, 1-(4-chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-yl, 1-(4-fluoro-phenyl)-3,5-dimethyl-1H-pyrazole-4-yl, 1H-benzotriazole-5-yl, 1H-indole-4-yl, 1H-indole-6-yl, 1-isopropyl-2-trifluoromethyl-1H-benzoimidazole-5-yl, 1-methyl-3-oxo-1,2,3,4-tetrahydro-quinoxaline-6-yl, 1-phenyl-5-trifluoromethyl-1H-pyrazole-4-yl, 2-(2-hydroxy-pyridin-4-yl)-1H-benzoimidazole-5-yl, 2-(4-cyano-phenyl)-1H-benzoimidazole-5-yl, 2,4-dimethyl-oxazole-5-yl, 2,4-dimethyl pyrimidine-5-yl, 2,4-dimethyl-thiazole-5-yl, 2,5-dimethyl-1H-pyrrole-3-yl, 2,5-dimethyl-1-phenyl-1H-pyrrole-3-yl, 2,5-dimethyl-1pyridin-4-ylmethyl-1H-pyrrolyl, 2,5-dimethyl-2H-pyrazole-3-yl, 2,6-dichloro-pyrid-3-yl, 2,6-dimethoxy-pyrid-3-yl, 2,6-dimethyl-pyrid-3-yl, 2-amino-4,6-dimethyl-pyrid-3-yl, 2-amino-6-chloro-pyrid-3-yl, 2-amino-pyrid-3-yl, 2-chloro-6-methyl-pyrid-3-yl, 2-chloro-pyrid-4-yl, 2-cyclopropyl-4-methyl-thiazole-5-yl, 2-dimethylamino-4-methyl-thiazole-5-yl, 2-dimethylamino-pyrid-4-yl, 2-ethyl-5-methyl-2H-pyrazole-3-yl, 2-hydroxy-6-methyl-pyrid-3-yl, 2-methyl-IH-benzoimidazole-5-yl, 2-methyl-3H-benzoimidazole-5-yl, 2-methyl-pyrid-3-yl, 2-methyl-6-trifluoromethyl-pyrid-3-yl, 2-methyl-thiazole-5-yl, 2-morpholin-4-yl-pyridin-4-yl, 2-morpholin-4-yl-pyrimidine-5-yl, 2-pyrrolidin-1-yl-pyridin-4-yl, 3,5-dimethyl-1H-pyrazole-4-yl, 3-amino-5,6-dimethyl-pyrazine-2-yl, 3-amino- 5 -methyl-pyrazine-2-yl, 3-amino-pyrazine-2-yl, 3-dimethylamino-4-methyl-phenyl, 3-dimethylamino-phenyl, 3H-benzoimidazole-5-yl, 1H-benzoimidazole-5-yl, 3-methanesulfonylainino-2-methyl-phenyl, 3-metbanesulfonylamino-phenyl, 3-methyl-isoxazole-4-yl, 3-morpholin-4-yl-phenyl, 3-piperidin-1-yl-phenyl, 3-pyrrolidin-1-yl-phenyl, 4-(2,2,2-trifluoro-ethoxy)-phenyl, 4,6-dimethyl-pyrid-3-yl, 4-amino-2-ethylsulfanyl-pyrimidine-5 -yl, 4-amino-2-methyl-pyrimidine-5-yl, 4-chloro-3-

methanesulfonylamino-phenyl, 4-chloro-3-sulfamoyl-phenyl, 4-methyl-3 -methylamino-phenyl, 4-methyl-thiazole-5-yl, pyridine-2-yl, pyridine-3-yl, pyridine-4-yl, 5-thiophen-2-yl-pyrid-3-yl, 2-methyl-4-trifluoromethyl-thiazol-5-yl, 5,6,7,8-tetrahydro-quinoline-3-yl, 5-amino-1-phenyl-1H-pyrazole-4-yl, 5-methanesulfonyl-2-methyl-phenyl, 5-methyl-1-phenyl-1H-pyrazole-4-yl, 5-methyl-isoxazole-3-yl, 5-methyl-pyrid-3-yl,5-methyl-pyrazine-2-yl, 6-chloro-pyrid-3-yl, 6-cyano-pyrid-3-yl, 6-dimethylamino-pyrid-3-yl, 6-ethynyl-pyrid-3-yl, 6-methoxymethyl-pyrid-3-yl, 6-methoxy-pyrid-3-yl,6-methyl-2-methylamino-pyrid-3-yl, 6-methylamino-pyrazine-2-yl, 6-methyl-pyrid-3-yl, 6-morpholin-4-yl-pyrid-3-yl, 6-pyrrolidin-1-yl-pyrid-3-yl, imidazo[1,2-a]pyridine-2-yl, 6-trifluoromethyl-pyrid-3-yl, and pyrimidine-4-yl.

[0173] Heteroaryl is preferably a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one, two or three heteroatoms selected from the group consisting of N, O, and S; heteroaryl is most preferably selected from the group consisting of: furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzoimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofaranyl, benzothiophenyl, and indazolyl.

[0174] The group Hetar is preferably a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one, two or three heteroatoms selected from the group consisting of N, O and S; the group Hetar is most preferably selected from the group consisting of. furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzoimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofuranyl, benzothiophenyl, and indazolyl.

[0175] Aryl is preferably phenyl.

[0176] m is preferably 0 or 2.

[0177] Compounds of the formula (I) used for the manufacture of a medicament for the stimulation of the expression of endothelial NO-synthase, in which one or more, including all of the above-mentioned groups have the preferred meanings, the more preferred meanings, the even more preferred meanings, the most preferred meanings or the particularly preferred meanings defined above are also an object of the present invention.

[0178] In a further embodiment, the object of the present invention is attained by compounds of the formula (I) in any of their stereoisomeric forms or mixtures thereof in any ratio or the pharmaceutically acceptable salts thereof used for the manufacture of a medicament for the stimulation of the expression of endothelial NO-synthase wherein the substituents R^1 to R^5, A, B and C and the groups aryl and heteroaryl have the following meanings.

[0179] R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl and C_2-C_{10}-alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)mercapto, CN, $COOR^6$, $CONR^7R^8$, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; R^9CO; $CONR^{10}R^{11}$; $COOR^{12}$; CF_3; halogens; pseudohalogens; $NR^{13}R^{14}OR^{15}$; $S(O)_mR^{16}$; $SO_2NR^{17}R^{18}$; and NO_2;

[0180] R^2 and R^3 are independently from each other selected from the group consisting of:

H; halogens; pseudohalogens; unsubstituted and at least monosubstituted C_1-C_6-alkyl. the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1-C_6-alkoxy; phenoxy; $S(O)mR^{19}$; CF_3; CN; NO_2; (C_1-C_6-alkyl)amino; di(C_1-C_6-alkyl)amino; (C_1-C_6-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH and phenyl-SO_2-O-, the substituents of which are selected from the group consisting of halogens, pseudohalogens, CH_3 and methoxy; (C_1-C_6-alkyl)SO_2-O-; unsubstituted and at least monosubstituted (C_1-C_6-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1-C_3-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1 -C_3-alkyl, halogens and methoxy;

[0181] A is CH_2, CHOH or CH-(C_1-C_3-alkyl);

[0182] B is CH_2 or CH-(C_1-C_3-alkyl);

[0183] C independently has the same meaning as B;

[0184] R_5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogens; pseudohalogens; C_1-C_{10}-alkyl; C_3-C_5-alkandiyl; phenyl; phenyl substituted C_1-C_4-alkyl; CF_3; OH; C_1-C_{10}-alkoxy; phenoxy; benzyloxy; CF_3O; (C_1-C_{10}-alkyl)COO; $S(O)_mR^{20}$; (C_1-C_{10}-alkyl)amino; di(C_1-C_{10}-alkyl)amino; (C_1-C_{10}-alkyl)-CONH-; (C_1-C_{10}-alkyl)-CON(C_1-C_3-alkyl)-; (C_1-C_{10}-alkyl)-CO; CF_3-CO; -OCH_2O-; -OCF_2O-; -OCH_2CH_2O-; -CH_2CH_2O-; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O, and S which can be substituted by one ore more substituents from the group consisting of halogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3; wherein all phenyl groups and phenyl-

containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3; where with respect to the group R^5 which can be an aryl or a heteroaryl. group, a heteroaryl group is generally preferred over an aryl group, and said heteroaryl group can be unsubstituted or substituted and carry at least one of the substituents mentioned above in the definition relating to R^5;

[0185] R^6 is H, C_1 -C_6-alkyl or benzyl;

[0186] R^7 is selected from the group consisting of:

H; C_1-C_6-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy and CF_3;

[0187] R^8 is H or C_1-C_6-alkyl;

[0188] R^9 is C_1-C_6-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1-C_3-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1-C_3-alkyl, C_1-C_3-alkoxy, halogens, pseudohalogens, and CF_3;

[0189] R^{10} independently has the same meaning as R^7;

[0190] R^{11} independently has the same meaning as R^8;

[0191] R^{12} independently has the same meaning as R^6;

[0192] R^{13} is selected from the group consisting of: H; C_1-C_6-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of

which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[0193] R^{14} is H or C_1-C_6-alkyl;

[0194] R^{15} is selected from the group consisting of: H; C_1-C_6-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substituents can be present;

[0195] R^{16} is selected from the group consisting of: C_1-C_6-alkyl; CF_3; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, pseudohalogens, C_1-C_3-alkyl, C_1-C_3-alkoxy, and CF_3, and wherein one or more of these substitutents can be present;

[0196] R^{17} independently has the same meaning as R^7;

[0197] R^{18} independently has the same meaning as R^8;

[0198] R^{19} independently has the same meaning as R^{16};

[0199] R^{20} independently has the same meaning as R^{16};

[0200] R^{21} independently has the same meaning as R^6;

[0201] R^{22} independently has the same meaning as R^7;

[0202] R^{23} independently has the same meaning as R^8;

[0203] R^{24} independently has the same meaning as R^7;

[0204] R^{25} independently has the same meaning as R^8;

[0205] heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O, and S;

[0206] aryl is phenyl, naphth-1-yl or naphth-2-yl;

[0207] m is 0, 1 or 2.

[0208] The compounds according to the general formula (I) can be used to upregulate the expression of the endothelial NO synthase and are helpful pharmaceutical compounds for the treatment of various diseases. In the context of the present invention, treatment includes the therapy as well as the prophylaxis of the respective diseases.

[0209] Examples of diseases which can be treated with the compounds according to the present invention include cardiovascular diseases like stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina (spasm), acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease (PAOD), endothelial dysfunction, atherosclerosis, restenosis, endothelial damage after PTCA, hypertension including essential hypertension, pulmonary hypertension, and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), erectile dysfunction, ventricular arrhythmia, and the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptives.

[0210] Compounds of the formula (I) can additionally be used in the therapy and prophylaxis of diabetes and diabetes complications (nephropathy, retinopathy), angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn.

[0211] Preferred indications are stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis and diabetes complications.

[0212] The compounds according to the formula (I) can also be used in combination with other pharmaceutically active compounds, preferably compounds which are able to enhance the effect of the compounds according to the general formula (I). Examples of

such compounds include: statins; ACE-inhibitors; AT1-antagonists; argininase-inhibitors; PDE V-inhibitors; Ca-antagonists; alpha-blockers; beta-blockers; metimazol and analogous compounds; arginine; tetrahydrobiopterin; vitamins, in particular vitamin C and vitamin B6; and niacin.

[0213] The compounds of the formula (I) and their pharmaceutically acceptable salts, optionally in combination with other pharmaceutically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the compounds of the formula (I) and their pharmaceutically acceptable salts for use as pharmaceuticals, their use as transcription stimulating agent for endothelial NO synthase and in particular their use in the therapy and prophylaxis of the above-mentioned syndromes as well as their use for preparing medicaments for these purposes. Furthermore, subjects of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise an effective dose of at least one compound of the formula (I) and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances and/or additives.

[0214] The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in

the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and on its severity.

[0215] The amount of compounds of the formula (I) and/or its pharmaceutically acceptable salts in the pharmaceutical preparations normally ranges from 0.2 to 800 mg, preferably from 0.5 to 500 mg, in particular from 1 to 200 mg, per dose, but depending on the type of the pharmaceutical preparation it may also be higher. The pharmaceutical preparations usually comprise 0.5 to 90 percent by weight of the compounds of the formula (I) and/or their pharmaceutically acceptable salts. The preparation of the pharmaceutical preparations can be carried out in a manner known per se. To this end, one or more compounds of the formula (I) and/or their pharmaceutically acceptable salts, together with one or more solid or liquid pharmaceutical carrier substances and/or additives (or auxiliary substances) and, if desired, in combination with other pharmaceutically active compounds having therapeutic or prophylactic action, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

[0216] For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or

hardened oils, etc. Suitable carriers for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of the formula (I) and their pharmaceutically acceptable salts and to use the resulting lyophilizates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

[0217] Besides the compound or compounds according to the invention and carriers, the pharmaceutical preparations can also contain additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

[0218] The dosage of the compound of the formula (I) to be administered and/or of a pharmaceutically acceptable salt thereof depends on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the therapy is acute or chronic or prophylactic, or on whether other active compounds are administered in addition to compounds of the formula (I). In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per kg

of bodyweight) is appropriate for administration to an adult weighing approximately 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, be divided into several, for example two, three or four individual doses. In some cases, depending on the individual response, it may be necessary to deviate upwards or downwards from the given daily dose.

[03] The compounds according to the formula (I) can also be used for other purposes than those indicated in the foregoing. Non-limiting examples include diagnostic purposes, use as biochemical tools, and as intermediates for the preparation of further compounds, e.g. pharmaceutically active compounds.

[0219] The present invention will now be illustrated in the following examples:

[0220] **Examples:**

[0221] **GENERAL PROCEDURES**

[0222] **Method A**

[0223] 0.5 mmol of the respective tetrahydronaphthyl amine were dissolved in 10 ml 1,2-dichloroethane, 41 μl(0.5 mmol) of pyridine were added, and then 1 ml of a 0.55 molar solution of the respective acid chloride in 1,2-dichloroethane was added at 0°C, followed by stirring over night at RT. The thus-obtained mixture was filtered, washed with 5% $NaHCO_3$- and 5% NaCl-solution, dried over sodium sulfate and concentrated. The thus-obtained residue was fractionated with prep. HPLC (RP18, acetonitrile/water, 0.1% trifluoroacetic acid).

[0224] Unless indicated otherwise, the retention times indicated were obtained on an Aglint HP 1100 MSD HPLC-system with an Alltech 33x7mm EPS C18 100Å 1.5 μm-column and a water/acetonitrile-gradient (start: 5% H_20/95% of a mixture or H_2O and acetonitrile

(10:90); 4.25min: 5% H_20/95% of a mixture or H_2O and acetonitrile (10:90); 4.5min: 5% H_20/95% of a mixture or H_2O and acetonitrile (10:90); 5 min: 5% H_20/95% of a mixture or H_2O and acetonitrile (10:90) and a flow of 0.75 ml/min.

[0225] There were thus obtained:

[0226] **EX 1: 4-Fluoro-N-(1,2,3,4-tetrahydro-naphth-2-yl)-benzamide**

[$M+H^+$] measured: 270.0

retention time: 5.07 min (gradient: from 10% acetonitrile to 90% acetonitrile in 10 min)

[0227] **EX 2: (R)-N-(6-Bromo-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 347.9

retention time: 3.26

[0228] **EX 3: (S)-N-(6-Bromo-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 347.9

retention time: 3.26

[0229] **EX 4: (R)-N-(8-Bromo-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 347.9

retention time: 3.25

[0230] **EX 5: (S)-N-(8-Bromo-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 347.9

retention time: 3.25

[0231] **EX 6: (R)-N-(5-Methoxy-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 300.0

retention time: 3.12

[0232] **EX 7: (S)-N-(5-Methoxy-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 300.0

retention time: 3.12

[0233] **EX 8: (S)-N-(7-Methoxy-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 300.0

retention time: 3.11

[0234] **EX 9: (R)-N-(8-Methoxy-1,2,3,4-tetrahydro-naphth-2-yl)-4-fluoro-benzamide**

[$M+H^+$] measured: 300.0

retention time: 3.13

[0235] **Method B:**

[0236] To 0.75 mmol of the respective acid and 271 µl (1.575 mmole) diisopropylethylamine (DIPEA) in 5 ml tetrahydrofuran were added 271 mg (0.825 mmol) O-[(cyano-ethoxycarbonylmethylene)-amino]-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) (dissolved in 1 ml DMF). After 15 min stirring at room temperature a mixture of 168 mg (0.900 mmol), 2-amino- 1,2,3,4-tetrahydronaphthalene hydrochloride in the form of the R- or S-enantiomer and 172 µl (1.000mmol) DIPEA in 1 ml DMF was added. After stirring for 6h the mixture was filtered and evaporated. The residue was taken up in ethyl acetate and washed successively with 20 ml 1n HCL and 20 ml 5% sodium hydrogencarbonate solution. The resulting organic phase was evaporated and purified via prep. HPLC. (RP 18, Acetonitrile/Water).

[0237] The chromatographic conditions (HPLC) were as follows: LiChroCart 55-2, PuroSpher STAR; RP 18 e (MERCK), solvent A: acetonitrile/water (90:10) + 0.5% formic acid; solvent B: acetonitrile/water (10:90) + 0.5% formic acid; gradient: 95% B 0,5 min, 95% B to 5% B in 1,75 min, 5% B 2,5 min; 1 ml/min.

[0238] **EX 10: 3-Dimethylamino-N-(R)-1,2,3,4-t trahydro-naphthalen-2-yl-benzamide**

[M+H$^+$] measured: 295

retention time: 3.020

[0239] **EX 11: 3-Dimethylamino-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-benzamide**

[M+H$^+$] measured: 295

retention time: 3.02

[0240] **EX 12: 3-Amino-pyrazine-2-carboxylic acid N-(R)- (1,2,3,4-tetrahydro-naphthalen-2-yl)-amide (salt with formic acid)**

[M+H$^+$] measured: 269

retention time: 3.03

[0241] **EX 13: 3-Amino-pyrazine-2-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide (salt with formic acid)**

[M+H$^+$] measured: 269

retention time: 3.03

[0242] **EX 14: 6-Chloro-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 287

retention time: 2.98

[0243] **EX 15: 6-Chloro-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 287

retention time: 2.99

[0244] **EX 16: 2-Hydroxy-6-methyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

$[M+H^+]$ measured: 283

Rf-value: 2.80

[0245] **EX 17: 2-Amino-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

$[M+H^+]$ measured: 283

retention time: 2.480

[0246] **EX 18: 2-Amino-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

$[M+H^+]$ measured: 268

retention time: 2.50

[0247] **EX 19: 6-Methyl-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

$[M+H^+]$ measured: 267

retention time: 2.61

[0248] **EX 20: 6-Methyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

$[M+H^+]$ measured: 267

retention time: 2.63

[0249] **EX 21: 1H-Indole-4-carboxylic acid-N-(R)- (1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

$[M+H^+]$ measured: 291

retention time: 2.963

[0250] **EX 22:** **1H-Indole-4-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 291

retention time: 2.97

[0251] **EX 23:** **1H-Benzoimidazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 292

retention time: 2.523

[0252] **EX 24:** **1H-Benzoimidazole-5-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 292

retention time: 2.54

[0253] **EX 25:** **1H-Benzotriazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 293

retention time: 2.806

[0254] **EX 26:** **1H-Benzotriazole-5-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 293

retention time: 2.78

[0255] **EX 27:** **2-Methyl-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide; salt with formic acid**

[M+H$^+$] measured: 267

retention time: 2.509

[0256] **EX 28: 2-Methyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

$[M+H^+]$ measured: 267

retention time: 2.46

[0257] **EX 29: 2,4-Dimethyl-thiazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

$[M+H^+]$ measured: 287

retention time: 2.920

[0258] **EX 30: 2,4-Dimethyl-thiazole-5-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

$[M+H^+]$ measured: 287

retention time: 2.93

[0259] **EX 31: 5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

$[M+H^+]$ measured: 332

retention time: 3.065

[0260] **EX 32: 5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

$[M+H^+]$ measured: 332

retention time: 3.08

[0261] **EX 33: 1-(4-Chloro-phenyl)-5-trifluoromethyl- 1 H-pyrazole-4-carboxylic acid N-(R)-(1,2,3,4-tetrahydro- naphthal n-2-yl)-amide**

$[M+H^+]$ measured: 420

retention time: 3.294

[0262] **EX 34: 1-(4-Chloro-phenyl)-5-trifluoromethyl-1H-pyrazole-4-carboxylic acid N- (S)-(1,2,3,4-tetrahydro- naphthalen-2-yl)-amide**

[$M+H^+$] measured: 420

retention time: 3.28

[0263] **EX 35: 5-Methyl-pyrazine-2-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide (salt with formic acid)**

[$M+H^+$] measured: 268

retention time: 2.987

[0264] **EX 36: 5-Methyl-pyrazine-2-carboxylic acid N-(S)-(l,2,3,4-tetrahydro-naphthalen-2-yl)-amide (salt with formic acid)**

[$M+H^+$] measured: 268

retention time: 3.00

[0265] **EX 37: 2,6-Dimetboxy-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

[$M+H^+$] measured: 313

retention time: 3.283

[0266] **EX 38: 2,6-Dimethoxy-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

[$M+H^+$] measured: 313

retention time: 3.24

[0267] **EX 39: 2-Chloro-6-methyl-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[$M+H^+$] measured: 301

retention time: 2.941

[0268] **EX 40: 2-Chloro-6-methyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 301

retention time: 2.97

[0269] **EX 41: 4-Methyl-2-phenyl-thiazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 349

retention time: 3.285

[0270] **EX 42: 4-Methy)-2-phenyl-thiazole-5-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 349

retention time: 3.31

[0271] **EX 43: 2-Amino-4,6-dimethyl-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide**

[M+H$^+$] measured: 296

retention time: 2.410

[0272] **EX 44: 2-Amino-4,6-dimethyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 296

retention time: 2.40

[0273] **EX 45: 2-Methyl-4-trifluoromethyl-thiazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2- yl)-amide**

[M+H$^+$] measured: 341

retention time: 3.076

[0274] **EX 46: 2-Methyl-4-trifluoromethyl-thiazole-5-carboxylic acid-N-(S)-(1,2,3,4-tetrahydro-naphthalen-2- yl)-amide**

[M+H$^+$] measured: 341

retention time: 3.07

[0275] **EX 47: 5-Trifluoromethyl-thieno[3,2-b]pyridine-6-carboxylic acid-N-(R)-(1,2,3,4-tetrahydro- naphthalen-2-yl)-amide (salt with formic acid)**

[M+H$^+$] measured: 377

retention time: 3.083

[0276] **EX 48: 1H-Indole-6-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 291

retention time: 2.990

[0277] **EX 49: 1H-Indole-6-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 291

retention time: 3.02

[0278] **EX 50: N-(R)-1,2,3,4-Tetrahydro-naphthalen-2-yl-6-trifluoromethyl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 321

retention time: 3.075

[0279] **EX 51:** **N-(S)-1,2,3,4-Tetrahydro-naphthalen-2-yl-6-trifluoromethyl -nicotinamide (salt with formic acid)**

[$M+H^+$] measured: 321

Rf-value: 3.09

[0280] **EX 52:** **2-Methyl-1H-benzoimidazole-5-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)- amide**

[$M+H^+$] measured: 306

retention time: 2.507

[0281] **EX 53:** **2-Methyl-1H-benzoimidazole-5-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[$M+H^+$] measured: 306

retention time: 2.46

[0282] **EX 54:** **2-Methyl-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-6-trifluoromethyl-nicotinamide (salt with formic acid)**

[$M+H^+$] measured: 335

retention time: 3.095

[0283] EX 55: **2-Methyl-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-6-trifluoromethyl-nicotinamide (salt with formic acid)**

[$M+H^+$] measured: 335

retention time: 3.10

[0284] **EX 56:** **6-Cyano-N-(R)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[$M+H^+$] measured: 278

retention time: 2.946

[0285] **EX 57: 6-Cyano-N-(S)-1,2,3,4-tetrahydro-naphthalen-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 278

retention time: 2.93

[0286] **EX 58: 3,5-Dimethyl-1H-pyrazole-4-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 270

retention time: 2.735

[0287] EX 59: **3,5-Dimethyl-1H-pyrazole-4-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 270

retention time: 2.76

[0288] **EX 60: 1-(4-Methoxy-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 362

retention time: 3.053

[0289] **EX 61: 1-(4-Methoxy-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 362

retention time: 3.06

[0290] **EX 62: N-(R)-1,2,3,4-Tetrahydro-naphthalen-2-yl-5-thiophen-2-yl-nicotinamide**

[M+H$^+$] measured: 335

retention time: 3.063

[0291] **EX 63: N-(S)-1,2,3,4-Tetrahydro-naphthalen-2-yl-5-thioph n-2-yl-nicotinamide (salt with formic acid)**

[M+H$^+$] measured: 335

retention time: 3.08

[0292] **EX 64: Benzo[c]isoxazole-3-carboxylic acid N-(R)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 293

retention time: 3.149

[0293] **EX 65: Benzo[c]isoxazole-3-carboxylic acid N-(S)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide**

[M+H$^+$] measured: 293

retention time: 3.17

[0294] **EX 66: 1-(3,5-Dichloro-phenyl)-5-propyl-1H-pyrazole-4-carboxylic acid N-(R)-(1,2,3,4-tetrahydro- naphthalen-2-yl)-amide**

[M+H$^+$] measured: 429

retention time: 3.558

[0295] **EX 67: 1-(3,5-Dichloro-phenyl)-5-propyl-1H-pyrazole-4-carboxylic acid N-(S)-(1,2,3,4-tetrahydro- naphthalen-2-yl)-amide**

[M+H$^+$] measured: 429

retention time: 3.54

[0296] **EX 68: (R)-N-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-isonicotinamid (salt with formic acid)**

[M+H$^+$] measured: 335

retention time: 2.695

[0297] **EX 69: (S)-N-(1,2,3,4-Tetrahydro-naphthalen-2-yl)-isonicotinamide (salt with formic acid)**

[M+H$^+$] measured: 335

retention time: 3.08

[0298] Measurement of activation of eNOS transcription

[0299] Activation of eNOS transcription was measured as described in detail in Li et al. "Activation of protein kinase C alpha and/or epsilon enhances transcription of the human endothelial nitric oxide synthase gene", Mol. Pharmacol. 1998; 53: 630-637. Briefly, a 3.5kB long fragment 5' of the starting codon of the eNOS gene was cloned, sequenced and cloned in firefly luciferase expression plasmids to monitor activation of the eNOS promoter by reporter gene activity. A human endothelial cell line stable transfected and expressing this promoter-reporter construct was used for compound testing. Cells were incubated for 18h with compounds.

[0300] All compounds were dissolved in sterile DMSO. A final concentration of 0.5% DMSO in complete medium was allowed. Induction of reporter gene expression in these cells was measured using a standard luciferase assay system (Promega, Cat. No E150) according to the manufacturer's instructions. Luciferase induction in cells incubated with compounds were compared to those incubated with solvent alone. The ratio of both activities (transcription induction ratio, TIR) was plotted as a function of compound concentration. Typically, TIR values started at low concentrations at a ratio of 1, indicating no compound effect, and extended up to a maximum TIR value TIR(max) which indicates

the increase of the eNOS transcription. EC50 values of transcription induction ratios as a function of compound concentration were determined graphically.

[0301] The effect of compounds on eNOS-transcription was confirmed in a second assay based on eNOS protein detection. Primary human umbilical vein cord endothelial cells (HUVEC) were isolated and cultivated according to standard procedures. Confluent cells were incubated with compounds for 18h and the effect on eNOS protein expression determined by a quantitative Western blotting procedure. After incubation with the compounds, HUVEC were lyzed in ice-cold lysis buffer containing 10mM Tris-HCl, pH 8.0, 1% SDS and protease inhibitors. The lyzate was subjected to a standard denaturating polyacrylamid gel electropheresis and blotted to nitrocellulose membranes. Using a specific primary monoclonal antibody (Transduction Laboratories, UK) and alkaline phosphatase labelled secondary antibody (Jackson Labs), a specific eNOS protein band was visualized and quantified based on a chemifluorescence detection method.

[04] The results are shown in the table below

Compound No:	**EC-50 (μM)**
1	2.2
4	>30
5	10
6	1.5
7	6
10	9.56
11	12.80

Compound No:	EC-50 (μM)
14	5.93
17	1.96
19	10.89
20	24.71
22	8.82
23	11.50
25	4.55
26	15.05
27	0.18
29	10.46
30	81.83
31	10.92
32	1.13
33	7.00
34	9.97
35	14.87
36	0.33
39	28.30
40	13.55
41	20.35

Compound No:	EC-50 (μM)
42	15.97
43	20.59
45	0.29
46	0.41
47	35.25
48	15.64
50	24.56
51	1.60
52	24.35
54	16.33
55	1.10
56	2.75
57	0.50
60	4.12
62	4.47
63	0.30
64	15.19
66	5.86
67	23.48
69	0.19

[0302] The effect of the compounds according to the invention can also be investigated in the following animal models. (Animal experiments are performed in accordance to the German animal protection law and to the guidelines for the use of experimental animals as given by the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health.)

[0303] Animals and Treatment (Experiments A - C)

[0304] ApoE and eNOS deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) are used. All animals are 10 - 12 weeks of age and weigh 22 to 28 g. Three days before surgery mice are divided into 4 groups (apoE control, n=10-12; apoE with test compounds, n=10-12; eNOS control, n=10-12; eNOS with test compounds, n=10-12) and receive either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol; in the following designated as placebo group) or a standard rodent chow + test compound (10 or 30 mg/kg/d p.o.).

[0305] **A Anti-hypertensive effect in ApoE knockout mice**

[0306] Blood-pressure is determined in conscious mice using a computerized tail-cuff system (Visitech Systems, Apex, Nc). After treatment of ApoE deficient mice and eNOS deficient mice with the test compounds the blood pressure is compared to the results obtained with a placebo treatment.

[0307] **B Inhibition of neointima formation and atherogenesis (femoral artery cuff)**

[0308] After a 3 day treatment of ApoE deficient mice with the respective compound, (10mg/kg/d pressed in chow), animals are anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg) followed by an intramuscular injection of xylazin (2 mg/kg) and a cuff is placed around the femoral artery as described in Moroi et al.(J Clin Invest.

101:1225-32, 1998). Briefly, the left femoral artery is dissected. A non-occlusive 2.0 mm polyethylene cuff made of PE-50 tubing (inner diameter 0.56 mm, outer diameter 0.965 mm, Becton Dickinson, Mountain View, Ca) is placed around the artery and tied in place with two 7-0 sutures. The right femoral artery is isolated from the surrounding tissues but a cuff is not placed. Treatment with the respective compound is continued for 14 days after surgery. Then the animals are sacrificed. The aorta are taken for determination of vascular eNOS expressions by quantitative western blotting. Both femoral arteries are harvested, fixed in formalin and embedded in paraffin. 20 cross sections (10 µm) are cut from the cuffed portion of the left femoral artery and from the corresponding segment of the right artery. Sections are subjected to standard hematoxylin and eosin staining. Morphometric analyses are performed using an image analysis computer program (LeicaQWin, Leica Imaging Systems, Cambridge, GB). For each cross section the area of the lumen, the neointima and the media are determined. To this end, the neointima is defined as the area between the lumen and the internal elastic lamina and the media is defined as the area between the internal and the external elastic lamina. The ratio between the area of the neointima and the area of the media is expressed as the neointima/media ratio. The results obtained in the compound group are compared to those obtained in the placebo group.

[0309] **C Prevention of atherosclerotic plaque formation in chronic treatment**

[0310] ApoE deficient mice are treated for 16 weeks with the respective compound pressed in chow and finally sacrificed. Aortas are removed from each mouse, fixed in formalin and embedded in paraffin. Plaque formation is measured via lipid lesions formation in the aortas (from aortic arch to diaphragm) and is analyzed by oil red O

staining. For quantifying the effect of the respective compound on vascular eNOS expression the femoral arteries are used in this experiment. The results obtained in the compound group are compared to those obtained in the placebo group.

[0311] **D Improvement of coronary function in diseased ApoE deficient mice**

[0312] Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) 6 month of age and weighing 28 to 36 g are used in the experiments. Mice are divided into 3 groups (C57BL/6, n=8; apoE control, n=8; apoE with respective compound, n=8) and receive for 8 weeks either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol) or a standard rodent chow + respective compound (30 mg/kg/d p.o.).

[0313] Mice are anesthetized with sodium pentobarbitone (100 mg/kg i.p.), and the hearts are rapidly excised and placed into ice-cold perfusion buffer. The aorta is cannulated and connected to a perfusion apparatus (HUGO SACHS ELECTRONICS, Freiburg, Germany) which is started immediately at a constant perfusion pressure of 60 min Hg. Hearts are perfused in a retrograde fashion with modified Krebs bicarbonate buffer, equilibrated with 95% O_2 and 5 % CO_2 and maintained at 37.5°C.

[0314] A beveled small tube (PE 50) is passed through a pulmonary vein into the left ventricle and pulled through the ventricular wall, anchored in the apex by a fluted end, and connected to a tip-micromanometer (Millar 1.4 French). The left atrium is cannulated through the same pulmonary vein and the heart switched to the working mode with a constant preload pressure of 10 mm Hg and an afterload pressure of 60 mm Hg. Aortic outflow and atrial inflow are continuously measured using ultrasonic flow probes (HSE/Transonic Systems Inc.). Coronary flow is calculated as the difference between atrial

flow and aortic flow. All hemodynamic data are digitized at a sampling rate of 1000 Hz and recorded with a PC using specialized software (HEM, Notocord).

[0315] Hearts are allowed to stabilize for 30 min. All functional hemodynamic data are measured during steady state, and during volume- and pressure loading.

[0316] Left ventricular function curves are constructed by varying pre-load pressure. For acquisition of preload curves, afterload is set at 60 mm Hg and preload is adjusted in 5 mm Hg steps over a range of 5 to 25 mm Hg. Hearts are allowed to stabilize at baseline conditions between pressure- and volume-loading.